$La_2(CO_3)_3$ search

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     FILE 'REGISTRY' ENTERED AT 14:27:05 ON 25 JAN 2003
L1            58 S LANTHANUM CARBONATE

     FILE 'CAPLUS' ENTERED AT 14:27:19 ON 25 JAN 2003
L2             1 S L1 (L) (BONE OR OSTEO? OR PAGET## OR ARTHRITIS OR ACHONDROPLA

     FILE 'REGISTRY' ENTERED AT 14:29:28 ON 25 JAN 2003
L3             1 S LANTHANUM CARBONATE/CN
L4            21 S LANTHANUM CARBONATE AND HYDRATE
L5            22 S L3 OR L4

     FILE 'WPIDS, MEDLINE, EMBASE' ENTERED AT 14:30:04 ON 25 JAN 2003

     FILE 'REGISTRY' ENTERED AT 14:30:16 ON 25 JAN 2003
                SET SMARTSELECT ON
L6           SEL L5 1- CHEM :      45 TERMS
                SET SMARTSELECT OFF

     FILE 'WPIDS, MEDLINE, EMBASE' ENTERED AT 14:30:19 ON 25 JAN 2003
L7            27 S L6/BI
L8            25 DUP REM L7 (2 DUPLICATES REMOVED)
L9             4 S L8 (L) (BONE OR OSTEO? OR PAGET## OR ARTHRITIS OR ACHONDROPL

=> d que l2; d que l9
L1            58 SEA FILE=REGISTRY LANTHANUM CARBONATE
L2             1 SEA FILE=CAPLUS L1 (L) (BONE OR OSTEO? OR PAGET## OR ARTHRITIS
                 OR ACHONDROPLASIA OR HYPERPARATHYROIDISM OR HYPOPHOSPHATASIA
                 OR FRIBROMATOUS OR FIBROUS DISPLAS? OR MYLTIPLE MYELOMA OR
                 RICKETS OR PERIODONTAL?)


L3             1 SEA FILE=REGISTRY LANTHANUM CARBONATE/CN
L4            21 SEA FILE=REGISTRY LANTHANUM CARBONATE AND HYDRATE
L5            22 SEA FILE=REGISTRY L3 OR L4
L6                SEL  L5 1- CHEM :      45 TERMS
L7            27 SEA L6/BI
L8            25 DUP REM L7 (2 DUPLICATES REMOVED)
L9             4 SEA L8 (L) (BONE OR OSTEO? OR PAGET## OR ARTHRITIS OR ACHONDROP
                 LASIA OR HYPERPARATHYROIDISM OR HYPOPHOSPHATASIA OR FRIBROMATOU
                 S OR FIBROUS DISPLAS? OR MYLTIPLE MYELOMA OR RICKETS OR
                 PERIODONTAL?)


=>
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L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN 2002:10286 CAPLUS
DN 136:64161
TI Lanthanum compounds for the treatment of bone diseases
IN Atherton, Nigel Derek; Totten, Joseph Wilson; Gaitonde, Michael David
PA Shire Holdings AG, Switz.
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002000227	A2	20020103	WO 2001-GB2836	20010626
	W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2001074341	A5	20020108	AU 2001-74341	20010626
	US 2002051822	A1	20020502	US 2001-891206	20010626
PRAI	GB 2000-15745	A	20000627		
	WO 2001-GB2836	W	20010626		

=> d 1-4 bib ab kwic

L9 ANSWER 1 OF 4 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-147852 [19] WPIDS
DNC C2002-045891
TI Use of lanthanum (III) compounds for enhancing bone formation, inhibiting osteoclastic differentiation and/or activating osteoblastic differentiation to treat bone disease such as osteoporosis.
DC B06
IN ATHERTON, N D; GAITONDE, M D; TOTTEN, J W
PA (SHIR-N) SHIRE HOLDINGS AG
CYC 96
PI WO 2002000227 A2 20020103 (200219)* EN 60p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002051822 A1 20020502 (200234)
AU 2001074341 A 20020108 (200235)
ADT WO 2002000227 A2 WO 2001-GB2836 20010626; US 2002051822 A1 US 2001-891206 20010626; AU 2001074341 A AU 2001-74341 20010626
FDT AU 2001074341 A Based on WO 200200227
PRAI GB 2000-15745 20000627
AB WO 200200227 A UPAB: 20020321
NOVELTY - Enhancing bone formation, inhibiting osteoclastic differentiation and/or activating osteoblastic differentiation to manage, treat or achieve prophylaxis of bone disease comprises administering a lanthanum compound (preferably lanthanum (III)) to a human or animal.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a composition for the treatment of a bone remodeling disorder comprising the lanthanum (III) compound and a bone enhancing agent.

ACTIVITY - Osteopathic; Cytostatic; Antiarthritic; Antirheumatic; Antiinflammatory.

MECHANISM OF ACTION - Osteoblast differentiation stimulator; Osteoclast differentiation inhibitor. 8-10 week old mice were killed and tibia and femora were dissected free from adhering soft tissues. The bone ends were cut off and the marrow was flushed with alpha -minimal essential medium (alpha -MEM) supplemented with penicillin (100 IU/ml) and streptomycin (100 micro g/ml). Cells were centrifuged for 10 minutes and the cell pellet was resuspended in alpha -MEM containing 10% fetal calf serum. Cells were then incubated for 2 hours at 370 deg. C.

Nonadherent cells were duly removed and the attached bone marrow cells were cultured (1 multiply 106 cells/well = 1 ml) for 6 days.

Half of the media were changed at day 3 and the treatments replaced. At the end of the culture, the plates were fixed with 2% paraformaldehyde in PBS for 20 minutes.

To study the effect of the lanthanum (III) ion on Osteoclast differentiation, the following groups were included:

(A) baseline (including vehicle);

(B) control (baseline without 1,25-dihydroxyvitamin D3);

(C) baseline + 100/500/1000/5000/15000 ng/ml lanthanum.

Six replicates were included in each group and the test was performed twice.

Osteoclast formation was determined by measuring tartrate-resistant acid phosphate (TRAP) activity from the culture media.

Combined results of relative TRAP 5b activities in three osteoclast differentiation assay were as follows: Osteoclast number for A) = 18; B) = 18; C) = 18/12/12/12/12 for 100/500/1000/5000/15000 ng/ml lanthanum respectively; Mean plus or minus SD for A) = 1 plus or minus 0.36; B) 0.15 plus or minus 0.07; C) = 0.70 plus or minus 0.27/0.89 plus or minus 0.29/0.65 plus or minus 0.23/0.05 plus or minus 0.20/0.30 plus or minus

0.19 for 100/500/1000/5000/15000 ng/ml lanthanum respectively.

The above data showed that a clear dose-dependent inhibition was observed with lanthanum (500 - 15000 ng/ml) that was statistically significant from lanthanum (1000 - 15000 ng/ml).

A statistically significant inhibition was also observed with lanthanum (100 ng/ml). In the control group where vitamin D was omitted, osteoclast differentiation was significantly lower than in the baseline group.

USE - For enhancing bone formation in a mammal (preferably human) having a bone deficit or risk of developing bone deficit or a bone remodeling disorder or is at risk of developing such disorder, e.g. osteoporosis, including primary, secondary, post-menopausal, male or steroid-induced osteoporosis, Paget's disease, osteoarthritis, rheumatoid arthritis, achondroplasia, osteochodrytis, hyperparathyroidism, osteogenesis imperfecta, congenital hypophosphatasia, fibromatous lesions, fibrous displasia, multiple myeloma, abnormal bone turnover, osteolytic bone disease, rickets, osteomalacia and periodontal disease; for treating a human having a bone fracture, bone trauma, or a condition associated with post-traumatic bone surgery, post-prosthetic joint surgery, post-plastic bone surgery, post-dental surgery, bone chemotherapy treatment or bone radiotherapy treatment.

In the preparation of a medicament for treating the above disease and conditions (all claimed).

ADVANTAGE - The lanthanum significantly enhances bone formation in vitro and vivo and also increases bone density in mammals. The lanthanum provides simultaneous actions of stimulating osteoblast differentiation and inhibiting osteoclast differentiation, and also activates bone formation activity of differentiated osteoclasts.

Dwg.0/4

TECH UPTX: 20020321

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Compound: The lanthanum (III) compound is lanthanum chloride, **lanthanum carbonate**, lanthanum salts, chelates or its derivatives, lanthanum resins or lanthanum absorbents (preferably **lanthanum carbonate** or lanthanum chloride).

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The **bone** enhancing agent is synthetic hormone, natural hormone, Oestrogen, calcitonin, tamoxifen, biphosphonate or its analog, vitamin D or its analog, mineral. . .

L9 ANSWER 2 OF 4 MEDLINE
AN 2000099280 MEDLINE
DN 20099280 PubMed ID: 10633463
TI Phosphate binders on iron basis: a new perspective?.
AU Hergesell O; Ritz E
CS Department of Internal Medicine, Ruperto Carola University, Heidelberg, Germany (FRG).
SO KIDNEY INTERNATIONAL. SUPPLEMENT, (1999 Dec) 73 S42-5. Ref: 31
Journal code: 7508622. ISSN: 0098-6577.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000209
Last Updated on STN: 20000309
Entered Medline: 20000128
AB Uremic patients on maintenance hemodialysis are in positive phosphate balance. This is mainly the result of the complex elimination kinetics of phosphate during dialysis. Removal of phosphate is less than net dietary intake. Classical phosphate binders such as calcium carbonate, calcium

acetate, and aluminum-based compounds are limited by side effects (hypercalcemia) and outright toxicity (aluminium). There have been numerous recent attempts to develop alternative phosphate binders, e.g., polyallylamine-hydrochloride (Renagel), **lanthanum carbonate**, and trivalent iron-containing compounds. The latter is based on old observations that iron salts may cause hyperphosphatemia and **rickets** in experimental animals and in patients. This idea has recently been taken up again, and effective inhibition of net intestinal phosphate uptake in non-uremic and uremic rats has been shown using simple iron salts (citrate, chloride, ammonium citrate) and complex compounds (cross-linked dextran and stabilized polynuclear iron hydroxide). In uremic rats, the latter compound reduces urinary phosphate excretion as an indicator of reduced intestinal phosphate uptake and has also been shown to be effective in subjects with preterminal renal failure. So far, no side effects or short-term toxicity has been observed. The compound appears promising and deserves further evaluation.

AB . . . effects (hypercalcemia) and outright toxicity (aluminium). There have been numerous recent attempts to develop alternative phosphate binders, e.g., polyallylamine-hydrochloride (Renagel), **lanthanum carbonate**, and trivalent iron-containing compounds. The latter is based on old observations that iron salts may cause hyperphosphatemia and **rickets** in experimental animals and in patients. This idea has recently been taken up again, and effective inhibition of net intestinal. . .

L9 ANSWER 3 OF 4 MEDLINE
AN 1999333213 MEDLINE
DN 99333213 PubMed ID: 10406555
TI Calcitriol, **lanthanum carbonate**, and other new phosphate binders in the management of renal **osteodystrophy**.
AU Hutchison A J
CS The Manchester Institute of Nephrology and Transplantation, The Royal Infirmary, UK.
SO PERITONEAL DIALYSIS INTERNATIONAL, (1999) 19 Suppl 2 S408-12. Journal code: 8904033. ISSN: 0896-8608.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990824
TI Calcitriol, **lanthanum carbonate**, and other new phosphate binders in the management of renal **osteodystrophy**.

L9 ANSWER 4 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000009024 EMBASE
TI Phosphate binders on iron basis: A new perspective?.
AU Hergesell O.; Ritz E.
CS Prof. E. Ritz, Department of Internal Medicine, University of Heidelberg, Bergheimer Strasse 56a, D-69115 Heidelberg, Germany
SO Kidney International, Supplement, (1999) 56/73 (S42-S45). Refs: 31
ISSN: 0098-6577 CODEN: KISUDF
CY United States
DT Journal; Article
FS 028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Uremic patients on maintenance hemodialysis are in positive phosphate

balance. This is mainly the result of the complex elimination kinetics of phosphate during dialysis. Removal of phosphate is less than net dietary intake. Classical phosphate binders such as calcium carbonate, calcium acetate, and aluminum-based compounds are limited by side effects (hypercalcemia) and outright toxicity (aluminium). There have been numerous recent attempts to develop alternative phosphate binders, e.g., polyallylamine-hydrochloride (Renagel), **lanthanum carbonate**, and trivalent iron-containing compounds. The latter is based on old observations that iron salts may cause hyperphosphatemia and **rickets** in experimental animals and in patients. This idea has recently been taken up again, and effective inhibition of net intestinal phosphate uptake in non-uremic and uremic rats has been shown using simple iron salts (citrate, chloride, ammonium citrate) and complex compounds (cross-linked dextran and stabilized polynuclear iron hydroxide). In uremic rats, the latter compound reduces urinary phosphate excretion as an indicator of reduced intestinal phosphate uptake and has also been shown to be effective in subjects with preterminal renal failure. So far, no side effects or short-term toxicity has been observed. The compound appears promising and deserves further evaluation.

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